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**MEMORANDUM**

SUBJECT: Arsenic Reference Values

FROM: Robert Benson, Ph.D.
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TO: David Mellard
ATSDR

This memo will reply to the comments directed at the document "Derivation of Short-term and Intermediate-term Reference Values for Arsenic, July 2000" contained in the ATSDR comments on EPA's baseline risk assessment for VBI70. The comments on the former document were separated out from the comments on the risk assessment document and were in the email to Peter Grevatt dated 09/29/2000.

**Exposure Duration Definitions**

There is a major disconnect between ATSDR and EPA on the definitions of exposure durations. I do not believe we will ever agree on a common set of definitions. EPA has not adopted definitions, but is considering adopting the following:

Acute: Exposure by the oral, dermal, or inhalation route for 24 hours or less.
Short term: Repeated exposure by the oral, dermal, or inhalation route for more than 24 hours up to 30 days.
Longer term: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days to approximately 10% of the life span in humans. (More than 30 days to approximately 90 days in rodent species).
Chronic: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans. (More than approximately 90 days to 2 years in rodent species).

ATSDR, on the other hand, has adopted the following definitions, which apply to both humans and laboratory animals:

Acute: Exposure for ≤14 days.
Intermediate: Exposure for 15-364 days.
Chronic: Exposure for ≥365 days.

The durations of exposure in the human studies available for arsenic did not fit easily into either Agency's scheme. Therefore, I used other definitions. These are:

Short-term: Exposure from one day to six months.
Intermediate-term: Exposure for six months to 10 years.

As far as I know neither Agency has definitions for "subacute" or "subchronic" exposure. In my opinion these terms should not be used, as they only confuse further an already difficult situation.

**Comments on Mazumder, 1998**

The data from exposure durations of 10-19 years are outside of my definitions and were not considered. For exposures of these durations, the chronic RfD would be more appropriate to use for a risk assessment.

I used the data from Table 4 for children ≤9 years old as only this group met the exposure definition. In tertile 1 there were no cases of keratosis or hyperpigmentation in males or females. In tertile 2 there were no cases of keratosis in males or females, no cases of hyperpigmentation in males, but 1 case of hyperpigmentation in the 28 females examined. As the prevalence of 1/28 (3.5%) does not reach statistical significance, I considered the exposure of 0.0032-0.0149 mg/kg-day to be a NOAEL in this study. In tertile 3 there are somewhat more cases with hyperpigmentation having the higher prevalence. For hyperpigmentation the prevalence for females is 3/32 (9.4%) and for males is 2/35 (5.7%). The authors provided no statistical evaluation of these data. However, the data for tertile 3 are close to being statistically significant and I consider this exposure (0.0149-0.0739 mg/kg-day) to be a marginal LOAEL. As this is only a marginal effect, I do not believe it is appropriate to consider the average exposure (0.044 mg/kg-day) as a LOAEL in this study.

**Comments on Zaldivar Studies**

I did not use the data for the 11 to 20 year old group as the exposure duration was outside of my definition. As far as I can tell from the reports, the majority of these children were born in 1952 or 1953. The study included data collected for 1968-1971. Exposure to arsenic from the drinking water did not start until 1958. Therefore, the average exposure presented in the papers for age groups ≥ 12-13 includes time when exposure to arsenic was very low and cannot be used.

The children that died has exposures during the first year of life of 0.13 mg/kg-day. There is no evidence that death occurs in these studies or other reports when the exposure is 0.06 mg/kg-day. While these data imply a steep exposure-response relationship, the data should not influence the assignment of a LOAEL of 0.05-0.06 mg/kg-day.

I choose not to use the data from Table 1 of Zaldivar and Ghai (1980) on exposure and prevalence rate. As far as I can tell, these are not independent data but a "breakout" from the data reported in Zaldivar (1977). For example, the prevalence rate for the 5 year old group in the 1980 publication was a predicted value from the regression equation.

**Comments on Chakraborti et al. (1999)**

I do not have a copy of this publication. I would appreciate getting a copy as I do not

have ready access to this journal. Because the paper contains no direct information on exposure duration, water consumption, or body weight, it would not meet my inclusion criteria.

**Comments on Cebrian, 1983**

The paper contains no reliable information on consumption of drinking water or body weight for children. The paper does contain information on drinking water consumption by adults (2.5 L/day for females and 3.5 L/day for males). EPA assumed a body weight of 55 kg and reported an estimated exposure of 0.022 mg/kg-day in the IRIS file. I choose to use information from the statistical analysis of drinking water consumption versus age from EPA's Exposure Factors Handbook to estimate the exposure to children of 0.04 mg/kg-day and consider this exposure close to a no effect level as there were no cases of hyperpigmentation or hyperkeratosis and one case of hypopigmentation in children 0-9 years. I think my approach for estimating exposure is more reliable than using ATSDR's default exposure factors of 2 liters per day and 30 kilograms which do not appear to be based on any objective data.